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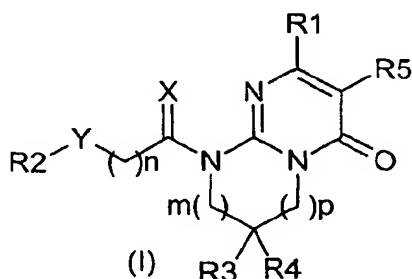
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(54) **Substituted 2-pyridinyl-6,7,8,9-tetrahydropyrimido(1,2-a)pyrimidin-4-one and
7-pyridinyl-2,3-dihydroimidazo(1,2-a)pyrimidin-5(1H)one derivatives**

(57) The invention relates to a pyrimidone derivative represented by formula (I) or a salt thereof wherein:

group, a C₁₋₄ alkoxy group, a benzyl group or a halogen atom;



X represents two hydrogen atoms, a sulphur atom, an oxygen atom or a C₁₋₂ alkyl group and a hydrogen atom;

Y represents a bond, an ethenylene group, an ethynylene group, an oxygen atom, a sulphur atom, a sulfonyl group, a sulfoxide group, a carbonyl group, a hydroxyiminomethylene group, a dioxolan group, a nitrogen atom being optionally substituted; or a methylene group optionally substituted;

R1 represents a 2, 3 or 4-pyridyl group optionally substituted by a C₃₋₆ cycloalkyl group, a C₁₋₄ alkyl

when Y represents a bond, a methylene group optionally substituted, a hydroxyiminomethylene group, a dioxolan group or a carbonyl group then R2 represents a C₁₋₆ alkyl group optionally; a C₃₋₆ cycloalkyl group, a C₁₋₄ alkylthio group, a C₁₋₄ alkoxy group, a C₁₋₂ perhalogenated alkyl group, a C₁₋₃ halogenated alkyl group, a phenylthio group, a benzyl group, a phenyl ring, a 5,6,7,8-tetrahydronaphthyl ring, a naphthyl ring, a pyridyl ring, a pyrrole ring, a thiophene ring, a furan ring or an imidazole ring;

when Y represents an ethenylene group, an ethynylene group, an oxygen atom, a sulphur atom, a sulfonyl group, a sulfoxide group or a nitrogen atom being optionally substituted then R2 represents a C₁₋₆ alkyl group optionally substituted by a hydroxy group, a C_{6,10} aryloxy or a C_{6,10} arylamino group; a C₃₋₆ cycloalkyl group, a C₁₋₂ perhalogenated alkyl group, a C₁₋₃ halogenated alkyl group, a benzyl group, a phenyl ring, a 5,6,7,8-tetrahydronaphthyl ring, a naphthyl ring, a C_{6,10} arylamino, a pyridyl ring, a pyrrole ring, a thiophene ring, a furan ring or an imidazole ring;

R3 and R4 represents, each independently, a hydrogen atom, a C₁₋₆ alkyl group, a hydroxy group, a C₁₋₄ alkoxy

group or a halogen atom;

R5 represents a hydrogen atom, a C₁₋₆ alkyl group or a halogen atom; with the proviso that when R3 and R4 represent each a hydrogen atom then R5 is not a hydrogen atom;

The invention relates also to a medicament comprising the said derivative or a salt thereof as an active

ingredient which is used for preventive and/or therapeutic treatment of a neurodegenerative disease caused by abnormal activity of GSK3 β or GSK3 β and cdk5/p25, such as Alzheimer disease.

Description

Technical Field

5 **[0001]** The present invention relates to compounds that are useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of neurodegenerative diseases caused by abnormal activities of GSK3 β alone or by the combined effects of GSK3 β and cdk5/p25.

Background Art

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[0002] GSK3 β (glycogen synthase kinase 3 β) is a proline directed serine, threonine kinase that plays an important role in the control of metabolism, differentiation and survival. It was initially identified as an enzyme able to phosphorylate and hence inhibit glycogen synthase. It was later recognized that GSK3 β was identical to tau protein kinase 1 (TPK1), an enzyme that phosphorylates tau protein in epitopes that are also found to be hyperphosphorylated in Alzheimer's disease and in several tauopathies. Interestingly, protein kinase B (AKT) phosphorylation of GSK3 β results in a loss of its kinase activity, and it has been hypothesized that this inhibition may mediate some of the effects of neurotrophic factors. Moreover, phosphorylation by GSK3 β of β -catenin, a protein involved in cell survival, results in its degradation by an ubiquitination dependent proteasome pathway. Thus, it appears that inhibition of GSK3 β activity may result in neurotrophic activity. Indeed there is evidence that lithium, a non-competitive inhibitor of GSK3 β , enhances neuritogenesis in some models and also increases neuronal survival, through the induction of survival factors such as Bcl-2 and the inhibition of the expression of proapoptotic factors such as P53 and Bax.

Recent studies have demonstrated that β -amyloid increases the GSK3 β activity and tau protein phosphorylation. Moreover, this hyperphosphorylation as well as the neurotoxic effects of β -amyloid are blocked by lithium chloride and by a GSK3 β antisense mRNA. These observations strongly suggest that GSK3 β may be the link between the two major pathological processes in Alzheimer's disease: abnormal APP (Amyloid Precursor Protein) processing and tau protein hyperphosphorylation.

Although tau hyperphosphorylation results in a destabilization of the neuronal cytoskeleton, the pathological consequences of abnormal GSK3 β activity are, most likely, not only due to a pathological phosphorylation of tau protein because, as mentioned above, an excessive activity of this kinase may affect survival through the modulation of the expression of apoptotic and antiapoptotic factors. Moreover, it has been shown that β -amyloid-induced increase in GSK3 β activity results in the phosphorylation and, hence the inhibition of pyruvate dehydrogenase, a pivotal enzyme in energy production and acetylcholine synthesis.

[0003] Cdk5/p25, also known as tau protein kinase 2 (TPK2), is a proline directed, Ser/Thr kinase essential for central nervous system development and in particular for neuronal migration and neurite outgrowth. Cdk5 is a homolog of cyclin-dependent kinases and rather ubiquitously expressed. Its activator p35 (a 305 aa protein) or a truncated form p25 (208 aa, missing an N-terminal proline-rich domain not required for activity) are selectively expressed in neurons, limiting cdk5 kinase activity essentially to the CNS. Cdk5 is completely inactive in the absence of p35 or p25. The term cdk5/p25 will be used here for the active enzyme since evidence exists suggesting that p25 and less so p35 may be involved in pathological processes.

40 **[0004]** Physiological substrates of cdk5/p25 include DARPP-32, Munc-18, PAK1, synapsin 1 and perhaps some others. In addition, it is now well established that cdk5/p25 phosphorylates tau protein epitopes which are hyperphosphorylated in Alzheimer's disease. More recently, elevated cdk5/p25 activity, mislocalization of cdk5 and an increase in p25 activator has been found in the brain of Alzheimer patients. Interestingly, prephosphorylation of tau protein by cdk5/p25 considerably enhances phosphorylation of tau by GSK3 β on other epitopes, also found hyperphosphorylated in Alzheimer's disease. Moreover, neurofibrillary tangles, the hallmark of Alzheimer's disease, are labeled with antisera for GSK3 β and cdk5, but not GSK3 α and MAP kinase, also, GSK3 β and cdk5 are associated with microtubules and both, more than PKA and CK, contribute to the AD-like phosphorylation of tau protein. These results taken together suggest that mixed inhibitors of GSK3 β and cdk5/p25 should be efficient in protecting tau protein from hyperphosphorylation. Therefore, they would be useful in the treatment of any pathological disorder associated with the abnormal phosphorylation of tau protein, in particular Alzheimer's disease, but also other tauopathies (e.g. frontotemporal dementia, corticobasal degeneration, Pick's disease, progressive supranuclear palsy).

50 **[0005]** Cdk5/p25 has been linked to apoptosis and neurodegeneration in more general terms. Its overexpression induces apoptosis in cultured neurons, in brain tissue apoptotic cells show strong immunoreactivity for cdk5. Neurotoxic agents, incl. A β (1-42), neuronal injury, ischemia or growth factor withdrawal lead to activation and mislocalization of cdk5/p25, abnormal phosphorylation of cdk5 substrates, cytoskeletal disruption and cell death. Moreover, phosphorylation by cdk5/p25 transforms DARPP-32 into an inhibitor of protein kinase A, reducing signal transduction in the striatum with obvious implications for Parkinson's disease. A role for cdk5 in ALS has also been proposed based on its ability to phosphorylate neurofilaments. More recently, deregulation of cdk5 was detected in a mouse model of

amyotrophic lateral sclerosis.

[0006] Altogether, these experimental observations indicate that GSK3 β inhibitors may find application in the treatment of the neuropathological consequences and the cognitive and attention deficits associated with Alzheimer's disease, as well as other acute and chronic neurodegenerative diseases. These include, in a nonlimiting manner, Parkinson's disease, tauopathies (e.g. frontotemporoparietal dementia, corticobasal degeneration, Pick's disease, progressive supranuclear palsy) and other dementia including vascular dementia; acute stroke and others traumatic injuries; cerebrovascular accidents (e.g. age related macular degeneration); brain and spinal cord trauma; peripheral neuropathies; retinopathies and glaucoma.

In addition GSK3 β inhibition may find application in the treatment of other diseases such as:

Non-insulin dependent diabetes (such as diabetes type II) and obesity; manic depressive illness; schizophrenia; alopecia; cancers such as breast cancer, non-small cell lung carcinoma, thyroid cancer, T or B-cell leukemia and several virus-induced tumors.

[0007] Since it appears that both, GSK3 β and cdk5/p25 play a major role in the induction of apoptosis in neuronal cells, combined inhibition of these two enzymes may find application in the treatment of not only Alzheimer's disease and the other above-mentioned tauopathies, but also in a number of other neurodegenerative disorders, in particular Parkinson's disease and amyotrophic lateral sclerosis; other dementias including vascular dementia; acute stroke and other traumatic injuries; cerebrovascular accidents (e.g. age related macular degeneration); brain and spinal cord trauma; peripheral neuropathies; retinopathies and glaucoma.

In addition mixed TPK1/TPK2 inhibitors may find their applications in the treatment of other diseases such as : smoking cessation and other withdrawal syndromes, epilepsy.

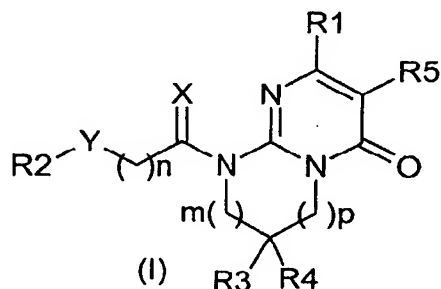
Disclosure of the Invention

[0008] An object of the present invention is to provide compounds useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of a disease caused by abnormal GSK3 β or GSK3 β and cdk5/p25 activity, more particularly of neurodegenerative diseases. More specifically, the object is to provide novel compounds useful as an active ingredient of a medicament that enables prevention and/or treatment of neurodegenerative diseases such as Alzheimer's disease.

[0009] Thus, the inventors of the present invention have identified compounds possessing inhibitory activity against GSK3 β . As a result, they found that compounds represented by the following formula (I) had the desired activity and were useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of the aforementioned diseases.

[0010] The present invention thus provides pyrimidone derivatives represented by formula (I) or salts thereof, solvates thereof or hydrates thereof:

wherein:



X represents two hydrogen atoms, a sulphur atom, an oxygen atom or a C₁₋₂ alkyl group and a hydrogen atom;

Y represents a bond, an ethenylene group, an ethynylene group, an oxygen atom, a sulphur atom, a sulfonyl group, a sulfoxide group, a carbonyl group, a hydroxyiminomethylene group, a dioxolan group, a nitrogen atom being optionally substituted by a C₁₋₆ alkyl group, a phenyl group or a benzyl group; or a methylene group optionally substituted by one or two groups chosen from a C₁₋₆ alkyl group, a benzyl group, a hydroxyl group, a C₁₋₄ alkoxy group, a C₁₋₂ perhalogenated alkyl group, an amino group, an actetyl amino group or a phenyl group;

R1 represents a 2, 3 or 4-pyridyl group optionally substituted by a C₃₋₆ cycloalkyl group, a C₁₋₄ alkyl group, a C₁₋₄ alkoxy group, a benzyl group or a halogen atom;

when Y represents a bond, a methylene group optionally substituted, a hydroxyiminomethylene group, a dioxolan group or a carbonyl group then R2 represents a C₁₋₆ alkyl group optionally substituted by a hydroxy group, a C_{6,10} aryloxy or a C_{6,10} arylamino group; a C₃₋₆ cycloalkyl group, a C₁₋₄ alkylthio group, a C₁₋₄ alkoxy group, a C₁₋₂ perhalogenated alkyl group, a C₁₋₃ halogenated alkyl group, a phenylthio group, a benzyl group, a phenyl ring, a 5,6,7,8-tetrahydronaphthyl ring, a naphthyl ring, a pyridyl ring, a pyrrole ring, a thiophene ring, a furan ring or an imidazole ring; the benzyl group or the rings being optionally substituted by 1 to 4 substituents selected from a C₁₋₆ alkyl group, a methylenedioxy group, a halogen atom, a C₁₋₂ perhalogenated alkyl group, a C₁₋₃ halogenated alkyl group, a hydroxyl group, a C₁₋₄ alkoxy group, a nitro, a cyano, an amino, a C₁₋₅ monoalkylamino group, a C₂₋₁₀ dialkylamino group, a C₁₋₆ alkylcarbonylamino group, a C_{6,10} arylcarbonylamino group, a C₁₋₄ alkylsulfonyl group, C₁₋₄ alkylsulfonyloxy group or a phenyl group;

when Y represents a ethenylene group, a ethynylene group, an oxygen atom, a sulphur atom, a sulfonyl group, a sulfoxide group or a nitrogen atom being optionally substituted then R2 represents a C₁₋₆ alkyl group optionally substituted by a hydroxy group, a C_{6,10} aryloxy or a C_{6,10} arylamino group; a C₃₋₆ cycloalkyl group, a C₁₋₂ perhalogenated alkyl group, a C₁₋₃ halogenated alkyl group, a benzyl group, a phenyl ring, a 5,6,7,8-tetrahydronaphthyl ring, a naphthyl ring, a C_{6,10} arylamino, a pyridyl ring, a pyrrole ring, a thiophene ring, a furan ring or an imidazole ring; the benzyl group or the rings being optionally substituted by 1 to 4 substituents selected from a C₁₋₆ alkyl group, a methylenedioxy group, a halogen atom, a C₁₋₂ perhalogenated alkyl group, a C₁₋₃ halogenated alkyl group, a hydroxyl group, a C₁₋₄ alkoxy group, a nitro, a cyano, an amino, a C₁₋₅ monoalkylamino group, a C₂₋₁₀ dialkylamino group, a C₁₋₆ alkylcarbonylamino group, a C_{6,10} arylcarbonylamino group, a C₁₋₄ alkylsulfonyl group, C₁₋₄ alkylsulfonyloxy group or a phenyl group;

R3 represents a hydrogen atom, a C₁₋₆alkyl group, a hydroxy group, a C₁₋₄ alkoxy group or a halogen atom;

R4 represents a hydrogen atom, a C₁₋₆alkyl group, a hydroxy group, a C₁₋₄ alkoxy group or a halogen atom;

R5 represents a hydrogen atom, a C₁₋₆ alkyl group or a halogen atom; with the proviso that when R3 and R4 represent each a hydrogen atom then R5 is not a hydrogen atom;

When m equals 0, p equals 1 or 2,

When m equals 1, p equals 0, 1 or 2,

When m equals 2, p equals 0 or 1;

and

n represents 0 to 3.

[0011] According to another aspect of the present invention, there is provided a medicament comprising as an active ingredient a substance selected from the group consisting of the pyrimidone derivatives represented by formula (I) and the physiologically acceptable salts thereof, and the solvates thereof and the hydrates thereof. As preferred embodiments of the medicament, there are provided the aforementioned medicament which is used for preventive and/or therapeutic treatment of diseases caused by abnormal GSK3 β or GSK3 β and cdk5/p25 activity, and the aforementioned medicament which is used for preventive and/or therapeutic treatment of neurodegenerative diseases and in addition other diseases such as:

Non-insulin dependent diabetes (such as diabetes type II) and obesity; manic depressive illness; schizophrenia; alopecia; smoking cessation and other withdrawal syndromes, epilepsy; cancers such as breast cancer, non-small cell lung carcinoma, thyroid cancer, T or B-cell leukemia and several virus-induced tumors.

[0012] As further preferred embodiments of the present invention, there are provided the aforementioned medicament wherein the diseases are neurodegenerative diseases and are selected from the group consisting of Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, tauopathies (e.g. frontotemporoparietal dementia, corticobasal degeneration, Pick's disease, progressive supranuclear palsy) and other dementia including vascular dementia; acute stroke and others traumatic injuries; cerebrovascular accidents (e.g. age related macular degeneration); brain and spinal cord trauma; peripheral neuropathies; retinopathies and glaucoma, and the aforementioned medicament in the form of pharmaceutical composition containing the above substance as an active ingredient together with one or more pharmaceutical additives.

[0013] The present invention further provides an inhibitor of GSK3 β or GSK3 β and cdk5/p25 activity comprising as an active ingredient a substance selected from the group consisting of the pyrimidone derivatives of formula (I) and the salts thereof, and the solvates thereof and the hydrates thereof.

[0014] According to further aspects of the present invention, there is provided a method for preventive and/or therapeutic treatment of neurodegenerative diseases caused by abnormal GSK3 β or GSK3 β and cdk5/p25 activity, which comprises the step of administering to a patient a preventively and/or therapeutically effective amount of a substance selected from the group consisting of the pyrimidone derivatives of formula (I) and the physiologically acceptable salts thereof, and the solvates thereof and the hydrates thereof; and a use of a substance selected from the group consisting of the pyrimidone derivatives of formula (I) and the physiologically acceptable salts thereof, and the solvates thereof and the hydrates thereof for the manufacture of the aforementioned medicament.

[0015] As used herein, the C₁₋₆ alkyl group represents a straight or branched alkyl group having 1 to 6 carbon atoms, for example, methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group, tert-butyl group, n-pentyl group, isopentyl group, neopentyl group, 1,1-dimethylpropyl group, n-hexyl group, isohexyl group, and the like;

The C₁₋₄ alkoxy group represents an alkyloxy group having 1 to 4 carbon atoms for example, methoxy group, ethoxy group, propoxy group, isopropoxy group, butoxy group, isobutoxy group, sec-butoxy group, tert-butoxy group, and the like;

The halogen atom represents a fluorine, chlorine, bromine or iodine atom;

The C₁₋₂ perhalogenated alkyl group represents an alkyl group wherein all the hydrogen have been substituted by a halogeno, for example a CF₃ or C₂F₅;

The C₁₋₃ halogenated alkyl group represents an alkyl group wherein at least one hydrogen has not been substituted by an halogen atom;

The C₁₋₅ monoalkylamino group represents an amino group substituted by one C₁₋₅ alkyl group, for example, methylamino group, ethylamino group, propylamino group, isopropylamino group, butylamino group, isobutylamino group, tert-butylamino group, pentylamino group and isopentylamino group;

The C₂₋₁₀ dialkylamino group represents an amino group substituted by two C₁₋₅ alkyl groups, for example, dimethylamino group, ethylmethylamino group, diethylamino group, methylpropylamino group and diisopropylamino group;

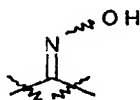
The C_{6,10} arylamino group represents an amino group substituted by a benzyl group and a naphthyl group;

The C_{6,10} aryloxy group represents a benzyloxy group and a naphthyloxy group.

The dioxolan group represents the following group :



The hydroxyiminomethylene group represents the following group :



[0016] The leaving group represents a group which could be easily cleaved and substituted, such a group may be for example a tosyl, a mesyl, a bromide and the like.

[0017] The compounds represented by the aforementioned formula (I) may form a salt. Examples of the salt include, when an acidic group exists, salts of alkali metals and alkaline earth metals such as lithium, sodium, potassium, magnesium, and calcium; salts of ammonia and amines such as methylamine, dimethylamine, trimethylamine, dicyclohexylamine, tris(hydroxymethyl)-aminomethane, *N,N*-bis(hydroxyethyl)piperazine, 2-amino-2-methyl-1-propanol, ethanolamine, *N*-methylglucamine, and L-glucamine; or salts with basic amino acids such as lysine, δ -hydroxylysine, and arginine. The base-addition salts of acidic compounds are prepared by standard procedures well known in the art.

[0018] When a basic group exists, examples include salts with mineral acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid; salts with organic acids such as methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, acetic acid, propionic acid, tartaric acid, fumaric acid, maleic acid, malic acid, oxalic acid, succinic acid, citric acid, benzoic acid, mandelic acid, cinnamic acid, lactic acid, glycolic acid, glucuronic acid, ascorbic acid, nicotinic acid, and salicylic acid; or salts with acidic amino acids such as aspartic acid, and glutamic acid.

The acid-addition salts of the basic compounds are prepared by standard procedures well known in the art which include, but are not limited thereto, dissolving the free base in an aqueous alcohol solution containing the appropriate acid and isolating the salt by evaporating the solution, or by reacting the free base and an acid in an organic solvent, in which case the salt separates directly, or is precipitated with a second organic solvent, or can be obtained by concentration of the solution. The acids which can be used to prepare the acid-addition salts include preferably those which produce, when combined with the free base, pharmaceutically-acceptable salts, that is, salts whose anions are relatively innocuous to the animal organism in pharmaceutical doses of the salts, so that the beneficial properties inherent in the free base are not compromised by side effects ascribable to the anions. Although medicinally acceptable salts of the basic compounds are preferred, all acid-addition salts are within the scope of the present invention.

[0019] In addition to the pyrimidone derivatives represented by the aforementioned formula (I) and salts thereof, their solvates and hydrates also fall within the scope of the present invention. The pyrimidone derivatives represented by the aforementioned formula (I) may have one or more asymmetric carbon atoms. As for the stereochemistry of such asymmetric carbon atoms, they may independently be in either (R) and (S) configuration, and the pyrimidone derivative may exist as stereoisomers such as optical isomers, or diastereoisomers. Any stereoisomers in pure form, any mixtures of stereoisomers, racemates and the like fall within the scope of the present invention.

[0020] Examples of preferred compounds of the present invention are shown in table 1 and table 2 hereinafter. However, the scope of the present invention is not limited by these compounds.

[0021] Preferred compounds of the present invention represented by formula (I) include also:

- (1) Compounds wherein R₁ represents a 3- or 4-pyridyl group and more preferably 4-pyridyl group, which may be substituted by a C₁₋₂ alkyl group, a C₁₋₂ alkoxy group or a halogen atom; and/or
- (2) X represents two hydrogen atoms, an oxygen atom or a C₁₋₂ alkyl group and a hydrogen atom;
- (3) Y represents a carbonyl group, a hydroxyiminomethylene group, a dioxolan group; or a methylene group optionally substituted by one or two groups chosen from a C₁₋₆ alkyl group, a benzyl group, a hydroxyl group, a C₁₋₄ alkoxy group, a C₁₋₂ perhalogenated alkyl group, an amino group, an acetylamino group, a phenyl group;

[0022] More preferred compounds of the present invention represented by formula (I) include also:

- (1) Compounds wherein R₁ represents an unsubstituted 4-pyridyl group;

[0023] Particularly preferred compounds of the present invention represented by formula (I) include compounds of table 1:

1. 9-[3-(2-fluorophenyl)-propyl]-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one
2. 9-(2-Oxo-2-phenyl-ethyl)-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one
3. 9-(2-Hydroxy-2-phenyl-ethyl)-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one
4. 9-(2-Oxo-2-phenyl-ethyl)-7,7-difluoro-2-pyridin-4-yl-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one
5. (-)-(S)-9-(2-Hydroxy-2-phenyl-ethyl)-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one
6. 9-(2-Oxo-2-phenyl-ethyl)-3-fluoro-7,7-difluoro-2-pyridin-4-yl-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one
7. 9-[2-Oxo-2-(3-chlorophenyl)-ethyl]-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one
8. (-)-(S)-9-(2-Hydroxy-2-phenyl-ethyl)-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one
9. 9-[2-Oxo-2-(3-fluorophenyl)-ethyl]-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one
10. 9-[2-Hydroxy-2-(3-chlorophenyl)-ethyl]-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one

EP 1 295 885 A1

11. 9-[2-Hydroxy-2-(3-fluorophenyl)-ethyl]-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
12. (-)-(S)-9-(2-Hydroxy-2-phenyl-ethyl)-3-fluoro-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
13. 9-[2-Oxo-2-(4-fluorophenyl)-ethyl]-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
14. 9-[2-Oxo-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl)-ethyl]-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
15. 9-[2-Oxo-2-(3-methoxyphenyl)-ethyl]-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
16. 9-[2-Oxo-2-(4-phenylphenyl)-ethyl]-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
17. 9-[2-(1-Methyl-2-oxo-2-(3,4-methylenedioxy-5-methoxyphenyl)-ethyl)]-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
18. 9-[2-Oxo-2-(4-chlorophenyl)ethyl]-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
19. 9-[2-Oxo-2-(naphth-2-yl)-ethyl]-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
20. 9-[2-Oxo-2-(4-methylphenyl)-ethyl]-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
21. 9-(2-Oxo-2-phenyl-ethyl)-7,7-dimethyl-3-bromo-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
22. (-)-(S)-9-(2-Methoxy-2-phenyl-ethyl)-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
23. 9-(3-Phenyl-propanoyl)-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
24. 9-(2-Hydroxy-2-methyl-2-phenyl-ethyl)-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
25. 9-(2-Methoxy-2-phenyl-2-trifluoromethyl-ethanoyl)-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
26. 9-(2-Hydroxy-2,2-diphenylethyl)-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
27. 9-(2-Hydroxyimino-2-phenyl-ethyl)-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
28. 9-(2-Hydroxy-2-methyl-2-phenyl-ethyl)-7,7-dimethyl-3-fluoro-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
29. 7,7-dimethyl-9-(2-phenyl-[1,3]dioxolan-2-ylmethyl)-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
30. 9-(2,3-dihydroxypropyl)-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one

EP 1 295 885 A1

31. (-)-(R)-(2-methoxy-2-phenyl-ethyl)-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
32. 9-(2-hydroxy-3-phenylaminopropyl)-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
33. 9-(2-acetylamino-2-phenyl-ethyl)-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
34. 9-(2-Amino-2-phenyl-ethyl)-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
35. 9-(2-hydroxy-3-phenoxypropyl)-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
36. 9-(2-Oxo-2-phenyl-ethyl)-3-fluoro-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
37. 9-[2-Oxo-2-(3-fluorophenyl)-ethyl]-3-fluoro-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
38. 9-(2-Oxo-2-phenyl-ethyl)-3-methyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
39. 9-(2-Oxo-2-phenyl-ethyl)-3-chloro-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
40. 9-(2-Oxo-2-phenyl-ethyl)-3-bromo-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
41. 2-(7-Methyl-6-oxo-8-pyridinyl-3,4-dihydro-2*H*,6*H* pyrimido[1,2-*a*]pyrimidin-1-yl)-*N*-phenyl-acetamide
42. (-)-(S)-9-(2-Hydroxy-2-phenyl-ethyl)-3-chloro-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
43. (-)-(S)-9-(2-Hydroxy-2-phenyl-ethyl)-3-methyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
44. (-)-(S)-9-(2-hydroxy-ethyl)-3-fluoro-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
45. (+)-(S)-9-(2-methoxy-2-phenyl-ethyl)-3-fluoro-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
46. (-)-(R)-9-(2-methoxy-2-phenyl-ethyl)-3-fluoro-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
47. 9-[3-(2-Fluorophenyl)propyl]-7-hydroxy-2-pyridin-4-yl-6,7,8,9-tetrahydro 4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
48. 9-[3-(2-Fluorophenyl)propyl]-7-methoxy-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
49. 9-(2-Oxo-2-phenyl-ethyl)-7-methyl-2-pyridin-4-yl-6,7,8,9-tetrahydro 4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
50. 9-(2-hydroxy-2-phenyl-ethyl)-7-methyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
51. 9-(2-hydroxy-2-methyl-phenyl-ethyl)-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
52. 9-(2-hydroxy-2-methyl-2-phenyl-ethyl)-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one

and compounds of table 2 :

1. [3-(2-Fluoro-phenyl)-propyl]-2,2-dimethyl-7-pyridin-4-yl-2,3-dihydro-1*H*-imidazo[1,2-*a*]pyrimidin-5-one

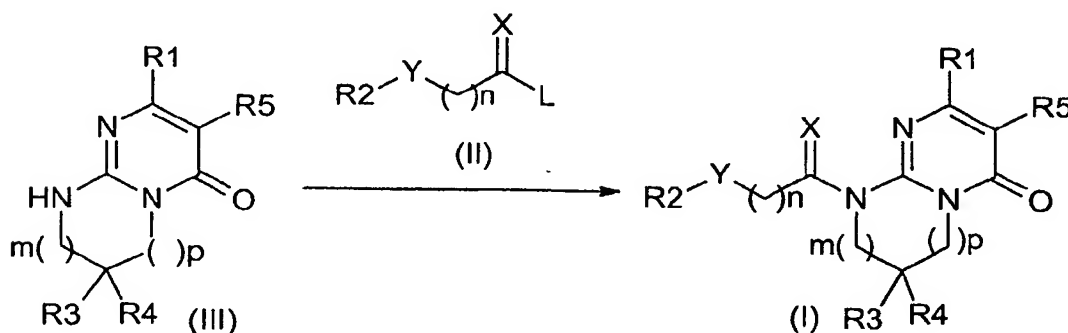
2. [2-Oxo-2-phenylethyl]-2,2-dimethyl-7-pyridin-4-yl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one
3. [2-Hydroxy-2-phenylethyl]-2,2-dimethyl-7-pyridin-4-yl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one
- 5 4. [2-Oxo-2-(4-chlorophenyl)ethyl]-2,2-dimethyl-7-pyridin-4-yl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one
5. [2-Oxo-2-(4-methylphenyl)ethyl]-2,2-dimethyl-7-pyridin-4-yl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one
- 10 6. [2-Oxo-4-phenylphenyl]-2,2-dimethyl-7-pyridin-4-yl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one
7. [1-Methyl-3-methoxy-2-(3,4-methylenedioxy-5-methoxyphenyl)-ethyl]-2,2-dimethyl-7-pyridin-4-yl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one
- 15 8. [2-Oxo-2-(napht-2-yl)-ethyl]-2,2-dimethyl-7-pyridin-4-yl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one
9. [2-Oxo-2-(4-fluorophenyl)-ethyl]-2,2-dimethyl-7-pyridin-4-yl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one
10. [2-Oxo-2-(3-methoxyphenyl)-ethyl]-2,2-dimethyl-7-pyridin-4-yl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one
- 20 11. [2-Oxo-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl)-ethyl]-2,2-dimethyl-7-pyridin-4-yl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one.

[0024] As a further object, the present invention concerns also methods for preparing the compounds represented by the aforementioned formula (I).

[0025] These compounds can be prepared, for example, according to methods explained below.

Preparation method

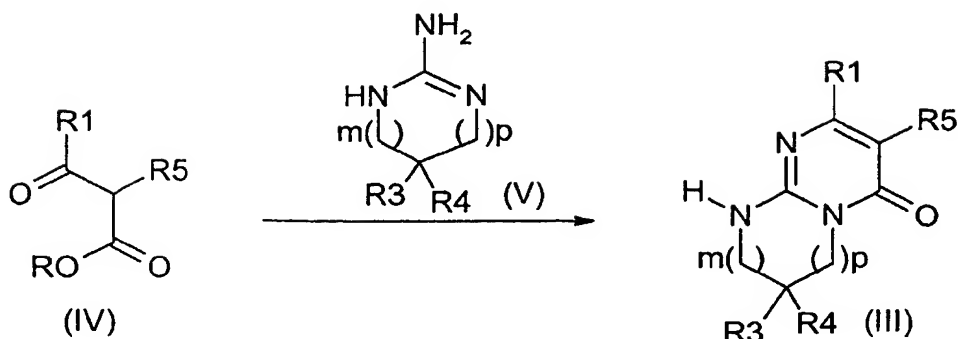
[0026] Pyrimidone compounds represented by the aforementioned formula (I) may be prepared according to scheme 1.



(In the above scheme the definition of R1, R2, R3, R4, R5, X, p, m and n are the same as those already described for compound of formula (I)).

[0027] The 7-pyridinylpyrimidin-5(1H)-one derivative represented by the above formula (III), wherein R1 is as defined for compound of formula (I), is allowed to react with a base such as sodium hydride, sodium carbonate or potassium carbonate in a solvent such as *N,N*-dimethylformamide, *N*-methylpyrrolidine, *N,N*-dimethylacetamide or chloroform at a suitable temperature ranging from 0 to 130°C under ordinary air, then with a compound of formula (II), wherein R2, X, Y and n are as defined for compound of formula (I) and L represents a leaving group preferably bromide or mesyl group, is added to obtain the compound of the aforementioned formula (I).

[0028] Compound of formula (II) are commercially available or may be synthesized according to well-known methods of one skilled in the art. The compound of formula (III) may be prepared according to the method defined in scheme 2.



(In the above scheme the definition of R1, R3, R4, R5, p and m are the same as already described.)

[0029] According to this method, the 3-ketoester of formula (IV) is allowed to react with a compound of formula (V). The reaction may be carried out in the presence of potassium carbonate, in an alcoholic solvent such as methanol, ethanol and the like or without, at a suitable temperature ranging from 25°-140°C under ordinary air.

[0030] Alternatively, compounds of formula (III) wherein R5 represents a hydrogen atom may be halogenated in order to give compounds of formula (III) wherein R5 is an halogen atom such as a bromine atom or a chlorine atom. The reaction may be carried out in an acidic medium such as acetic acid or propionic acid, in presence of bromosuccinimide or chlorosuccinimide, or bromine.

[0031] In addition, compounds of formula (III) wherein R5 represents a fluorine atom may be obtained by analogy to the method described in Tetrahedron Letters, Vol.30, N°45, pp 6113-6116, 1989.

[0032] Compounds of formula (V) or (IV) are commercially available or may be synthesized according to well-known methods of one skilled in the art.

[0033] For example compounds of formula (IV), wherein R1 represent a pyridyl group optionally substituted by a C₁₋₄ alkyl group, C₁₋₄ alkoxy group or a halogen atom, can be prepared by reacting a nicotinic acid optionally substituted by a C₁₋₄ alkyl group, C₁₋₄ alkoxy group or an halogen, with a malonic acid monoester. The reaction can be carried out using methods well known to one skilled in the art, such as for example in presence of a coupling agent such as 1,1'-carbonylbis-1H-imidazole in a solvent such as tetrahydrofuran at a temperature ranging from 20 to 70°C.

[0034] Compounds of formula (I) may also be obtained starting from another compound of formula (I) using well-known methods of one skilled in the art.

[0035] In the above reactions, protection or deprotection of a functional group may sometimes be necessary. A suitable protecting group Pg can be chosen depending on the type of the functional group, and a method described in the literature may be applied. Examples of protecting groups, of protection and deprotection methods are given for example in Protective groups in Organic Synthesis Greene et al., 2nd Ed. (John Wiley & Sons, Inc., New York).

[0036] The compounds of the present invention have inhibitory activity against GSK3β. Accordingly, the compounds of the present invention are useful as an active ingredient for the preparation of a medicament, which enables preventive and/or therapeutic treatment of a disease caused by abnormal GSK3β or GSK3β and cdk5/p25 activity and more particularly of neurodegenerative diseases such as Alzheimer's disease. In addition, the compounds of the present invention are also useful as an active ingredient for the preparation of a medicament for preventive and/or therapeutic treatment of neurodegenerative diseases such as Parkinson's disease, amyotrophic lateral sclerosis, tauopathies (e. g. frontotemporoparietal dementia, corticobasal degeneration, Pick's disease, progressive supranuclear palsy) and other dementia including vascular dementia; acute stroke and others traumatic injuries; cerebrovascular accidents (e. g. age related macular degeneration); brain and spinal cord trauma; peripheral neuropathies; retinopathies and glaucoma; and other diseases such as non-insulin dependent diabetes (such as diabetes type II) and obesity; manic depressive illness; schizophrenia; alopecia; smoking cessation and other withdrawal syndromes, epilepsy; cancers such as breast cancer, non-small cell lung carcinoma, thyroid cancer, T or B-cell leukemia and several virus-induced tumors.

[0037] The present invention further relates to a method for treating neurodegenerative diseases caused by abnormal activity of GSK3β or GSK3β and cdk5/p25 and of the aforementioned diseases which comprises administering to a mammalian organism in need thereof an effective amount of a compound of the formula (I).

[0038] As the active ingredient of the medicament of the present invention, a substance may be used which is selected from the group consisting of the compound represented by the aforementioned formula (I) and pharmacologically acceptable salts thereof, and solvates thereof and hydrates thereof. The substance, per se, may be administered as the medicament of the present invention, however, it is desirable to administer the medicament in a form of a pharmaceutical composition which comprises the aforementioned substance as an active ingredient and one or more phar-

maceutical additives. As the active ingredient of the medicament of the present invention, two or more of the aforementioned substances may be used in combination. The above pharmaceutical composition may be supplemented with an active ingredient of another medicament for the treatment of the above mentioned diseases. The type of pharmaceutical composition is not particularly limited, and the composition may be provided as any formulation for oral or parenteral administration. For example, the pharmaceutical composition may be formulated, for example, in the form of capsules, syrups, emulsions, suspensions, solutions and the like, or in the form of pharmaceutical compositions for parenteral administrations such as injections for intravenous, intramuscular, or subcutaneous administration, drip infusions, transdermal preparations, transmucosal preparations, nasal drops, inhalants, suppositories and the like. Injections or drip infusions may be prepared as powdery preparations such as in the form of lyophilized preparations, and may be used by dissolving just before use in an appropriate aqueous medium such as physiological saline. Sustained-release preparations such as those coated with a polymer may be directly administered intracerebrally.

[0039] Types of pharmaceutical additives used for the manufacture of the pharmaceutical composition, content ratios of the pharmaceutical additives relative to the active ingredient, and methods for preparing the pharmaceutical composition may be appropriately chosen by those skilled in the art. Inorganic or organic substances, or solid or liquid substances may be used as pharmaceutical additives. Generally, the pharmaceutical additives may be incorporated in a ratio ranging from 1 % by weight to 90% by weight based on the weight of an active ingredient.

Examples of excipients used for the preparation of solid pharmaceutical compositions include, for example, lactose, sucrose, starch, talc, cellulose, dextrin, kaolin, calcium carbonate and the like. For the preparation of liquid compositions for oral administration, a conventional inert diluent such as water or a vegetable oil may be used. The liquid composition may contain, in addition to the inert diluent, auxiliaries such as moistening agents, suspension aids, sweeteners, aromatics, colorants, and preservatives. The liquid composition may be filled in capsules made of an absorbable material such as gelatin. Examples of solvents or suspension mediums used for the preparation of compositions for parenteral administration, e.g. injections, suppositories, include water, propylene glycol, polyethylene glycol, benzyl alcohol, ethyl oleate, lecithin and the like. Examples of base materials used for suppositories include, for example, cacao butter, emulsified cacao butter, lauric lipid, witepsol.

[0040] The dose and frequency of administration of the medicament of the present invention are not particularly limited, and they may be appropriately chosen depending on conditions such as a purpose of preventive and/or therapeutic treatment, a type of a disease, the body weight or age of a patient, severity of a disease and the like. Generally, a daily dose for oral administration to an adult may be 0.01 to 1,000 mg (the weight of an active ingredient), and the dose may be administered once a day or several times a day as divided portions, or once in several days. When the medicament is used as an injection, administrations may preferably be performed continuously or intermittently in a daily dose of 0.001 to 100 mg (the weight of an active ingredient) to an adult.

Chemical Examples

[0041] The present invention will be explained more specifically with reference to the following general examples, however, the scope of the present invention is not limited to these examples.

Example 1 (Compound N°8 of table 1)

(-)-(S)-9-(2-Hydroxy-2-phenyl-ethyl)-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one hydrochloride (1:1)

1.1 7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one

[0042] A mixture of 5.9g (30.55 mmol) of ethyl 3-(4-pyridyl)-3-oxopropionate, 5.0g (30.55 mmol) of 5,5-dimethyl-1,4,5,6-tetrahydro-2-pyrimidinamine monohydrochloride

(prepared according to US Patent No. 4,262,122 and 6.33g (45.82 mmol) of potassium carbonate in 60ml of ethanol was heated at reflux temperature during 12 h. The cooled suspension was filtered and the solvent removed by evaporation. The residue obtained was dissolved in dichloromethane and washed with water. The organic phase was dried and evaporated to give 6.30g (80%) of product as a beige solid. Mp.: 152-154°C.

1.2. (-)-(S)-9-(2-Hydroxy-2-phenyl-ethyl)-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one hydrochloride (1:1)

[0043] A suspension of 0.8g (3.12 mmol) of 7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one in 8ml of anhydrous dimethylformamide was treated with 274mg (6.86mmol) of sodium hydride (60% sus-

EP 1 295 885 A1

pension in mineral oil) and the resulting mixture was heated at 50°C for 30 min. 0.494ml (3.74 mmol) of (S)-2-chloro-1-phenylethanol was added and the reaction mixture was heated at 50°C during 4h.

The cooled solution was treated with water and extracted with ethyl acetate. The organic phase was dried and evaporated to give crude product, which was purified by silica gel chromatography, eluting with dichloromethane/methanol in the proportions 98/2 to 90/10. The 0.486g of pure product obtained in the form of free base was dissolved in hot ethanol and treated with 1 equivalent of hydrogen-chloride in isopropanol. The cooled solution was filtered to afford 0.192 g (15%) of white solid. Mp : 234-236°C. $[\alpha]_D^{22.9}$ (c=1, MeOH)

Example 2 (Compound N°49 of table 1)

9-(2-Oxo-2-phenyl-ethyl)-7-methyl-2-pyridin-4-yl-6,7,8,9-tetrahydro 4H-pyrimido[1,2-a]pyrimidin-4-one

2.1 5-Methyl-1,4,5,6-tetrahydro-2-pyrimidinamine hydrochloride

[0044] To a solution containing 6.7g (41.6 mmol) of 2-methyl-1,3-propandiamine hydrochloride (Tetrahedron (1994) 50(29), 8617-8632) in 50ml of methanol was added 83ml of a solution of sodium methylate in methanol (1mmol/ml) and the resulting mixture treated with 3.97g (41.6 mmol) of guanidine hydrochloride. The reaction mixture was heated at 140°C for 3h.

The solution was filtered, the solvent evaporated and the residue obtained was used directly in the next step.

2.2 7-Methyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one

[0045] The product was obtained by analogy with step N° 1.1 and using the intermediate from step N°2.1.

2.3 9-(2-Oxo-2-phenyl-ethyl)-7-methyl-2-pyridin-4-yl-6,7,8,9-tetrahydro 4H-pyrimido[1,2-a]pyrimidin-4-one

[0046] A suspension of 0.32g (1.34 mmol) of 7-methyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one in 10ml of anhydrous dimethylformamide was treated with 64mg (1.34mmol) of sodium hydride (50% suspension in mineral oil) and the resulting mixture was stirred for 40 min. 0.267g (1.34 mmol) of phenacyl bromide was added and the reaction mixture stirred at room temperature for 2h.

The solution was treated with water and extracted with ethyl acetate. The organic phase was dried and evaporated to give crude product, which was purified by silica gel chromatography, eluting with dichloromethane/methanol in the proportions 100/0 to 90/10 to give 0.235g of pure product obtained in the form of free base. Mp : 202-203°C.

Example 3 (Compound N°47 of table 1)

9-[3-(2-Fluorophenyl)propyl]-7-hydroxy-2-pyridin-4-yl-6,7,8,9-tetrahydro 4H-pyrimido[1,2-a]pyrimidin-4-one

3.1 7-Hydroxy-2-pyridin-4-yl-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one

[0047] The product was obtained by analogy with step N° 1.1 and using 2-amino-1,4,5,6-tetrahydro-5-pyrimidinol (Arch.Int.Pharmacodyn.Ther. (1968), 175(1), 193-211). Mp. : 305-307°C.

3.2 9-[3-(2-Fluorophenyl)propyl]-7-hydroxy-2-pyridin-4-yl-6,7,8,9-tetrahydro 4H-pyrimido[1,2-a]pyrimidin-4-one

[0048] A suspension of 1.0g (4.09 mmol) of 7-hydroxy-2-pyridin-4-yl-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one and 0.95g (4.09 mmol) of 1-[3-(methylsulfonyloxy)propyl]-2-fluorobenzene in 100ml of anhydrous acetonitrile was treated with 4.1g (1.42 mmol) of potassium fluoride suspended on alumina (Fluka) and the resulting mixture was heated at 80 °C for 24h.

The cooled solution was filtered and the solvent evaporated to leave a residue which was purified by silica gel chromatography, eluting with dichloromethane/methanol/ammonia in the proportions 98/2/0.2 to 96/4/0.4. 0.96g (61%) of pure product was obtained in the form of free base. Mp : 205-207°C.

Example 4 (Compound N°48 of table 1) 9-[3-(2-Fluorophenyl)propyl]-7-methoxy-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one oxalate (1:1)

4.1 9-[3-(2-Fluorophenyl)propyl]-7-methoxy-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one oxalate (1:1)

[0049] To a suspension containing 0.12g (0.31 mmol) of 9-[3-(2-fluorophenyl)propyl]-7-hydroxy-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one in 3ml of dimethylformamide was added 14mg (0.34 mmol) of a suspension of sodium hydride in mineral oil (60%) and the resulting mixture was stirred at room temperature for 15min. The mixture was cooled to -20°C and treated with 19.6μL (0.31 mmol) of iodomethane. Stirring was continued for 1h. Water was added and the organic phase was separated. The solvent was evaporated to leave a residue which was purified by silica gel chromatography, eluting with dichloromethane/methanol/ammonia in the proportions 98/2/0.2. 0.1g (85%) of pure product was obtained and transformed into a monooxalate salt by treatment with one equivalent of oxalic acid 0.085g (65%). Mp : 164-166°C.

Example N°5 (Compound N°4 of table 1) 9-(2-Oxo-2-phenyl-ethyl)-7,7-difluoro-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one

5.1 5,5-Difluoro-1,4,5,6-tetrahydro-2-pyrimidinamine

[0050] The product was obtained by analogy with the method described in 2.1 and using 2,2-difluoro-1,3-propandiamine (Tetrahedron (1994) 50(29), 8617-8632) and was used as such in the next step.

5.2 7,7-difluoro-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one

[0051] The product was obtained by analogy with step N° 1.1 and using the intermediate from step N°5.2. Mp. : 239-240°C.

5.3 9-(2-Oxo-2-phenyl-ethyl)-7,7-difluoro-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one

[0052] By analogy with the method described in step N°2.3 the compound was obtained as a free base. Mp. : 217-219°C.

Example 6 (Compound N° 6 of table 1) 9-(2-Oxo-2-phenyl-ethyl)-3-fluoro-7,7-difluoro-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one hydrochloride (1:1)

6.1 Ethyl 4-pyridyl-3-oxo-2-fluoropropanoate hydrochloride (cf. Tetrahedron Letters, Vol.30,N°45,pp 6113-6116, 1989)

[0053] To a solution of 134,88 ml (0.54 mol) of tri-*n*-butylphosphine in 500 ml of anhydrous tetrahydrofuran under argon was added 63.8 ml (0.54 mol) of ethyl bromofluoroacetate and the resulting mixture stirred at room temperature during 40 h.

The reaction mixture was cooled to -78°C and 237,58 ml (0.594 mol) of *n*-butyl lithium (2.5M in hexane) was added dropwise and allowed to stir for 1 h.

76.44 g (0.54 mol) of isonicotinoyl chloride (Heterocyclic Chemistry, 18, 519, 1981) was added and the mixture allowed to stir for 1 h.

The temperature was allowed to increase to room temperature during the night and at 0°C, 700 ml of a 5% aqueous solution of sodium bicarbonate was added and the resulting mixture allowed to stir overnight. The tetrahydrofuran was evaporated under reduced pressure and the resulting aqueous phase was extracted with dichloromethane, washed with brine and dried over anhydrous sodium sulfate and evaporated to give a dark brown residue. Flash chromatography on silica gel (eluant cyclohexane/ethyl acetate 90/10 to 50/50). This product was treated with a solution of hydrochloric acid in isopropanol (6N) to give 20 g (17%) of product. Mp. 142-144 °C.

6.2 7,7-Dimethyl-3-fluoro-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one

[0054] A mixture of 5.0g (20.19 mmol) of ethyl 4-pyridyl-3-oxo-2-fluoropropanoate hydrochloride, 3.30g (20.19 mmol) 5,5-dimethyl-1,4,5,6-tetrahydro-2-pyrimidinamine hydrochloride (prepared according to US Patent No. 4262122 and 8.37g (60.57 mmol) of potassium carbonate in 30ml of ethanol were heated at reflux temperature during 18 h.

The cooled suspension was filtered and the solvent removed by evaporation. The residue obtained was treated with dichloromethane and washed with water. The organic phase was dried and evaporated to give 1.9g (34%) of product as a beige solid. Mp. : 190-192°C.

6.39-(2-Oxo-2-phenyl-ethyl)-3-fluoro-7,7-difluoro-2-pyridin-4-yl-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one hydrochloride (1:1)

[0055] A suspension of 0.30g (1.09 mmol) of 7,7-dimethyl-3-fluoro-2-pyridin-4-yl-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one in 6ml of anhydrous dimethylformamide was treated with 53mg (1.31 mmol) of sodium hydride (60% suspension in mineral oil) and the resulting mixture was stirred for 10 min. 0.261 g (1.31 mmol) of phenacyl bromide was added and the reaction mixture stirred at room temperature for 3h.

The solution was treated with water and extracted with ethyl acetate. The organic phase was dried and evaporated to give crude product, which was purified by silica gel chromatography, eluting with dichloromethane/methanol in the proportions 98/2 to 90/10 to give 0.10g of pure product obtained in the form of free base which was transformed into the hydrochloride salt. Mp : 236-238°C.

Example 7 (Compound N°21 in table 1) 9-(2-Oxo-2-phenyl-ethyl)-7,7-dimethyl-3-bromo-2-pyridin-4-yl-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one

7.1 3-Bromo-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one hydrobromide (1:1)

[0056] To a solution of 3.0g (11.7 mmol) of 7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one in 75ml of acetic acid was added dropwise 0.6ml (11.7 mmol) of bromine. The mixture was allowed to stir at room temperature for 2h.

The precipitated solid was recovered by filtration, washed with ether and dried affording 4.53g (97%) of product as a yellow solid. Mp.: 270-272°C.

9-(2-Oxo-2-phenyl-ethyl)-7,7-dimethyl-3-bromo-2-pyridin-4-yl-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one

[0057] A solution containing 4.15g (10.43 mmol) of 3-bromo-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one hydrobromide in water was treated with an excess of an aqueous solution of sodium hydroxide. The free base was extracted with dichloromethane and the organics dried and evaporated. The residue was solubilized in 25ml of anhydrous dimethylformamide and 0.542g (13.56 mmol) of sodium hydride (60% suspension in mineral oil) and the resulting mixture was stirred for 40 min. 2.43g (12.49 mmol) of phenacyl bromide was added and the reaction mixture stirred at room temperature for 5h.

The solution was treated with water at 0°C and the precipitate which formed was recovered by filtration and dried, 3.5g (74%). Mp : 223-225°C.

Example 8 (Compound N°38 in table 1) 9-(2-Oxo-2-phenyl-ethyl)-3-methyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one

8.1 3-Methyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one

[0058] A mixture of 14.0g (67.56 mmol) of ethyl 2-methyl-3-(4-pyridyl)-3-oxopropionate (prepared according to French Patent Fr 2529786), 9.16g (67.66 mmol) of 1,4,5,6-tetrahydro-2-pyrimidinamine monohydrochloride (prepared according to J.Org.Chem. 1955, 20, 829) and 9.33g (67.66 mmol) of potassium carbonate in 300ml of ethanol was heated at reflux temperature during 12 h. The cooled suspension was filtered and the solvent removed by evaporation. The residue obtained was treated with water and the precipitate filtered and dried. The product was thus obtained as a brown solid. 10.5g (64%) Mp. : 242-243°C.

8.2 9-(2-Oxo-2-phenyl-ethyl)-3-methyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one

[0059] A suspension of 0.25g (1.03 mmol) of 3-methyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one in 4ml of anhydrous dimethylformamide was treated with 45mg (1.03mmol) of sodium hydride (50% suspension in mineral oil) and the resulting mixture was stirred for 1 h. 0.205g (1.03 mmol) of phenacyl bromide was added and the reaction mixture stirred at room temperature for 5h. The solution was treated with water and extracted with ethyl acetate. The organic phase was dried and evaporated to give crude product, which was purified by silica gel chromatography, eluting with dichloromethane/methanol/ammonia in the proportions 98/2/0.2 to give 0.10g (27%) of pure

product obtained in the form of free base. Mp : 190-192°C.

Example 9 (Compound N°2 in table 1) 9-(2-Oxo-2-phenyl-ethyl)-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one hydrochloride(1:1)

[0060] The product was obtained by using the method described in step 2.3 and employing 7,7-dimethyl-2-pyridin-4-yl- 6,7,8,9- tetrahydro-4H-pyrimido [1,2-a]pyrimidin-4-one. Mp. : 283-285°C.

Example 10 (Compound N°3 in table 1) (+/-)9-(2-Hydroxy-2-phenyl-ethyl)-7,7 dimethyl-2-pyridin-4-yl- 6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one

[0061] To a solution of 2.0g (5.34 mmol) of 9-(2-Oxo-2-phenyl-ethyl)-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one obtained in step 9 in 100ml of methanol at 0°C was added 0.24g (6.41 mmol) of sodium borohydride. Stirring was maintained for 30min. and the solvent was removed by evaporation.

Water was added and the resulting mixture extracted with dichloromethane. The organics were dried and evaporated and the residue was triturated with ethyl acetate to give 1.66g (83%) of product. The Z-but-2-endoate salt of the product was characterized. Mp. : 195-197°C.

Example 11 (Compound N°34 in table 1) 9-(2-Amino-2-phenyl-ethyl)-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one hydrochloride (1:1)

11.1 2-[2-(3,3-Dimethyl-6-oxo-8-pyridin-4-yl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-yl)-1-phenyl-ethyl]-isoindole-1,3-dione

[0062] To a solution of 0.2g (0.531 mmol) of 9-(2-Hydroxy-2-phenyl-ethyl)-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one, 0.080g (0.584 mmol) of phthalimide and 0.195g (0.742 mmol) in 30ml of anhydrous tetrahydrofuran at 0°C was added 0.142ml (0.903 mmol) of diethyl azodicarboxylate and the reaction mixture stirred for 18h.

The solvent was evaporated and the residue was purified by chromatography on silica gel eluting with dichloromethane/methanol/diethylamine in the proportions 98/2/0.2 to give 0.06g (22%) of product.

11.2 9-(2-Amino-2-phenyl-ethyl)-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one hydrochloride (1:1)

[0063] A solution of 0.470g (0.929 mmol) of 2-[2-(3,3-dimethyl-6-oxo-8-pyridin-4-yl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-yl)-1-phenyl-ethyl]-isoindole-1,3-dione in 50ml of ethanol containing 0.452ml (9.29 mmol) of hydrazine hydrate was heated at reflux temperature for 18h.

The cooled solution was filtered and the solvent removed by evaporation. The residue was purified by chromatography on silica gel eluting with ethyl acetate/methanol/diethylamine in the proportions 95/5/0.5 to 94/6/0.6. The free base recovered was transformed into the hydrochloride salt to give 0.283g (68%) of product. Mp. : 227-231°C.

Example 12 (Compound N°1 in table 2) [3-(2-Fluoro-phenyl)-propyl]-2,2-dimethyl-7-pyridin-4-yl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one hydrochloride (1:2)

12.1 5,5-Dimethyl-4,5-dihydro-1H-imidazol-2-ylamine hydrobromide (1:1)

[0064] To a solution of 15g (0.17 mol) of 1,2-diamino-2-methylpropane in 150ml of water at 0°C, was added 18g (0.17 mol) of cyanogen bromide portionwise and the temperature was allowed to warm to room temperature during 4h. The water was removed by evaporation and ethanol was added and evaporated. Trituration in a mixture of diethyl ether and ethanol gave 29.5g (89%) of product as an amorphous hygroscopic solid.

12.2 2,2-Dimethyl-7-pyridin-4-yl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one

[0065] A suspension of 4.5g (23.2 mmol) of 5,5-dimethyl-4,5-dihydro-1H-imidazol-2-ylamine hydrobromide, 2.99g (15.46 mmol) of ethyl 3-(4-pyridyl)-3-oxopropionate and 4.27g (30.89 mmol) of potassium carbonate in 100ml of ethanol was heated at reflux temperature for 18h.

The cooled suspension was filtered and the solvents evaporated. The residue obtained was dissolved in dichloromethane and washed with water. The solvent was evaporated to give 2.5g (67%) of pure product. Mp. : 226-228°C.

12.3 [3-(2-Fluoro-phenyl)-propyl]-2,2-dimethyl-7-pyridin-4-yl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one hydrochloride (1:2)

[0066] A suspension of 0.3g (1.23 mmol) of 2,2-dimethyl-7-pyridin-4-yl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one in 6ml of anhydrous dimethylformamide was treated with 64mg (1.6 mmol) of sodium hydride (60% suspension in mineral oil). The mixture was heated at 60°C for 10min. and then 0.322g (1.48 mmol) of 3-(2-fluorophenyl)propyl bromide was added and the mixture heated at 120°C during 1h.

The cooled solution was treated with water and extracted with ethyl acetate. The solvent was evaporated to leave a residue which was purified by silica gel chromatography, eluting with dichloromethane/methanol in the proportions 98/2 to 95/5 to obtain 0.248g (55%) of pure product was obtained in the form of free base which was transformed into the dihydrochloride salt Mp : 140-142°C.

[0067] A list of chemical structures and physical data for compounds of the aforementioned formula (I) illustrating the present invention is given in tables 1 and 2. The compounds have been prepared according to the methods of the example.

[0068] In the tables, R1 is an unsubstituted 4-pyridyl group (4-py), Ph represents a phenyl group, (S) or (R) indicate in the column "Y" the stereochemistry respectively (S) or (R) of the carbon atom; in the column "X", when X represents two hydrogen atoms, only "H" is indicated and in table 1, for compounds of formula (I) "m" and "p" equal 1; In table 2, for compounds of formula (I), "m" equals 0 and "p" equals 1.

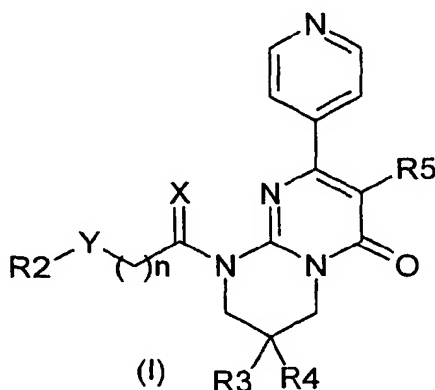

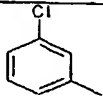



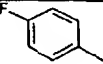
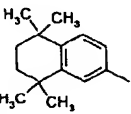

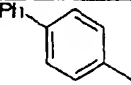
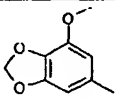
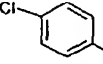
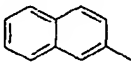
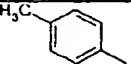
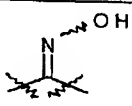
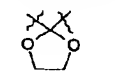
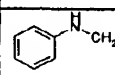
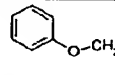
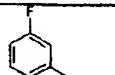
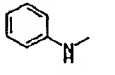




Table 1

N°	X	Y	R2	R3	R4	R5	n	Mp °C	salt
1	H	CH ₂		CH ₃	CH ₃	H	1	250-252	(1:1) hydro-chloride
2	H	CO	Ph	CH ₃	CH ₃	H	0	283-285	(1:1) hydro-chloride
3	H	CH(OH) Racemate	Ph	CH ₃	CH ₃	H	0	195-197	(1:1) (Z)-but-2-enedioate
4	H	CO	Ph	F	F	H	0	217-219	Free base
5	H	CH(OH) (S)	Ph	F	F	H	0	179-180	Free base
6	H	CO	Ph	CH ₃	CH ₃	F	0	236-238	(1:1) hydro-chloride
7	H	CO		CH ₃	CH ₃	H	0	238-240	(1:1) hydro-chloride
8	H	CH(OH) (-)-(S)	Ph	CH ₃	CH ₃	H	0	234-236	(1:1) hydro-chloride
9	H	CO		CH ₃	CH ₃	H	0	233-235	(1:1) hydro-chloride
10	H	CH(OH) Racemate		CH ₃	CH ₃	H	0	195-197	Free base

N°	X	Y	R2	R3	R4	R5	n	Mp °C	salt
11	H	CH(OH) Racemate		CH ₃	CH ₃	H	0	198-199	Free base
12	H	CH(OH) (-)-(S)	Ph	CH ₃	CH ₃	F	0	228-230	(1:1) hydro- chloride
13	H	CO		CH ₃	CH ₃	H	0	256-257	(1:1) hydro- chloride
14	H	CO		CH ₃	CH ₃	H	0	237-238	(1:1) hydro- chloride
15	H	CO		CH ₃	CH ₃	H	0	203-204	(1:1) hydro- chloride
16	H	CO		CH ₃	CH ₃	H	0	232-233	(1:1) hydro- chloride
17	H,CH ₃ (rac.)	CO		CH ₃	CH ₃	H	0	241-242	(1:1) hydro- chloride
18	H	CO		CH ₃	CH ₃	H	0	257-258	(1:1) hydro- chloride
19	H	CO		CH ₃	CH ₃	H	0	232-233	(1:1) hydro- chloride
20	H	CO		CH ₃	CH ₃	H	0	256-257	(1:1) hydro- chloride
21	H	CO	Ph	CH ₃	CH ₃	Br	0	223-225	Free base
22	H	CH(OMe) (S)	Ph	CH ₃	CH ₃	H	0	145-146	Free base
23	O	CH ₂	Ph	CH ₃	CH ₃	H	1	134-136	Free base
24	H	C(OH)(CH ₃) racemate	Ph	CH ₃	CH ₃	H	0	208-210	Free base
25	O	C(OMe)(CF ₃) racemate	Ph	CH ₃	CH ₃	H	0	162-163	Free base
26	H	C(OH)(Ph) racemate	Ph	CH ₃	CH ₃	H	0	270-272	Free base

N°	X	Y	R2	R3	R4	R5	n	Mp °C	salt
27	H		Ph	CH ₃	CH ₃	H	0	249-250	Free base
28	H	C(OH)(CH ₃) racemate	Ph	CH ₃	CH ₃	F	0	230-232	(1:1) hydro-chloride
29	H		Ph	CH ₃	CH ₃	H	0	214-215	Free base
30	H	CH(OH) racemate	CH ₂ OH	CH ₃	CH ₃	H	0	242-243	(1:1) hydro-chloride
31	H	C(H)(OMe) (-)-(R)	Ph	CH ₃	CH ₃	H	0	190-192	(1:1) hydro-chloride
32	H	C(H)(OH) racemate		CH ₃	CH ₃	H	0	199-200	Free base
33	H	C(H)(NHAc) racemate	Ph	CH ₃	CH ₃	H	0	246-247	Free base
34	H	C(H)(NH ₂) racemate	Ph	CH ₃	CH ₃	H	0	227-231	(1:1) hydro-chloride
35	H	C(H)(OH) racemate		CH ₃	CH ₃	H	0	156-157	Free base
36	H	CO	Ph	H	H	F	0	264-266	(1:1) hydro-chloride
37	H	CO		H	H	F	0	260-262	(1:1) hydro-chloride
38	H	CO	Ph	H	H	CH ₃	0	190-192	Free base
39	H	CO	Ph	H	H	Cl	0	260-262	(1:1) hydro-chloride
40	H	CO	Ph	H	H	Br	0	260-262	(1:1) hydro-chloride
41	H	CO		H	H	CH ₃	0	242-243	Free base
42	H	C(H)(OH) (-)-(S)	Ph	H	H	Cl	0	221-213	(1:1) hydro-chloride
43	H	C(H)(OH) (S)	Ph	H	H	CH ₃	0	211-213	(1:1) hydro-chloride

N°	X	Y	R2	R3	R4	R5	n	Mp °C	salt
44	H	C(H)(OH) (-)-(S)	Ph	H	H	F	0	170-172	(1:1) hydro- chloride
45	H	C(H)(OMe) (+)-(S)	Ph	H	H	F	0	108-110	(1:1) hydro- chloride
46	H	C(H)(OMe) (-)-(R)	Ph	H	H	F	0	202-204	(1:1) hydro- chloride
47	H	CH ₂		H	OH (rac)	H	1	205-207	Free base
48	H	CH ₂		H	OMe (rac)	H	1	164-166	(1:1) oxalate
49	H	CO	Ph	H	CH ₃ (rac)	H	0	202-203	Free base
50	H	C(H)(OH) racemate	Ph	H	CH ₃ (rac)	H	0	174-175	Free base
51	H	C(OH)(CH ₃) chiral	Ph	CH ₃	CH ₃	H	0	150-151	Free base
52	H	C(OH)(CH ₃) chiral	Ph	CH ₃	CH ₃	H	0	144-146	Free base

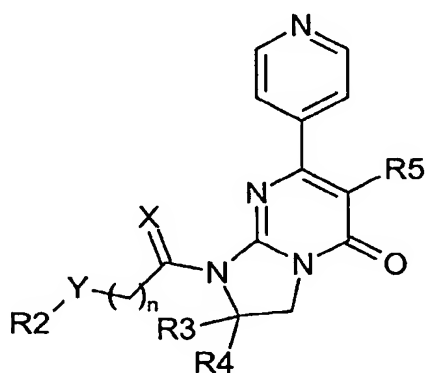







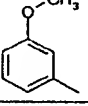
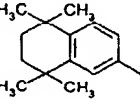


Table 2

N°	X	Y	R2	R3	R4	R5	n	Mp °C	Salt
1	H	CH ₂		CH ₃	CH ₃	H	1	140-142	(1:1) hydro-chloride
2	H	CO	Ph	CH ₃	CH ₃	H	0	314-316	(1:1) hydro-chloride
3	H	C(H)(OH) (rac.)	Ph	CH ₃	CH ₃	H	0	173-175	base
4	H	CO		CH ₃	CH ₃	H	0	268-269	(1:1) hydro-chloride
5	H	CO		CH ₃	CH ₃	H	0	252-253	(1:1) hydro-chloride
6	H	CO		CH ₃	CH ₃	H	0	230-231	(1:1) hydro-chloride
7	H,CH ₃ (rac.)	CO		CH ₃	CH ₃	H	0	259-260	(1:1) hydro-chloride
8	H	CO		CH ₃	CH ₃	H	0	186-187	(1:1) hydro-chloride
9	H	CO		CH ₃	CH ₃	H	0	249	(1:1) hydro-chloride
10	H	CO		CH ₃	CH ₃	H	0	233	(1:1) hydro-chloride
11	H	CO		CH ₃	CH ₃	H	0	250-251	(1:1) hydro-chloride

Test Example: Inhibitory activity of the medicament of the present invention against GSK3β:

[0069] Two different protocols can be used.

[0070] In a first protocol : 7.5 μM of prephosphorylated GS1 peptide and 10 μM ATP (containing 300,000 cpm of 33P-ATP) were incubated in 25 mM Tris-HCl, pH 7.5, 0.6 mM DTT, 6 mM MgCl₂, 0.6 mM EGTA, 0.05 mg/ml BSA buffer for 1 hour at room temperature in the presence of GSK3beta (total reaction volume : 100 microliters).

[0071] In a second protocol : 4.1 μM of prephosphorylated GS1 peptide and 42 μM ATP (containing 260,000 cpm 33P-ATP) were incubated in 80 mM Mes-NaOH, pH 6.5, 1 mM Mg acetate, 0.5 mM EGTA, 5 mM 2-mercaptoethanol, 0.02% Tween 20, 10% glycerol buffer for 2 hours at room temperature in the presence of GSK3beta.

Inhibitors were solubilised in DMSO (final solvent concentration in the reaction medium, 1%).

[0072] The reaction was stopped with 100 microliters of a solution made of 25 g polyphosphoric acid (85% P₂O₅), 126 ml 85% H₃PO₄, H₂O to 500 ml and then diluted to 1:100 before use. An aliquot of the reaction mixture was then transferred to Whatman P81 cation exchange filters and rinsed with the solution described above. Incorporated 33P radioactivity was determined by liquid scintillation spectrometry.

The phosphorylated GS-1 peptide had the following sequence :

NH₂-YRRAAVPPSPSLSRHSSPHQS(P)EED-⁺COOH.

[0073] The GSK3β inhibitory activity of the compounds of the present invention are expressed in IC₅₀, and as an

illustration the range of IC_{50} 's of the compounds in table 1 is between 5 nanomolar to 2 micromolar concentrations and of the compounds in table 2 is between 30 nanomolar to 2 micromolar concentrations.

Test Example 2: Inhibitory activity of the medicament of the present invention against cdk5/p25:

[0074] The following protocol may be used :

[0075] 0.4 mg/ml Histone H1 and 10 μ M ATP (containing 300,000 cpm of ^{33}P -ATP) were incubated in 50 mM Hepes, pH 7.2, 1 mM DTT, 1 mM $MgCl_2$, 1 mM EGTA, 0.02% Tween 20 buffer for 1 hour at room temperature in the presence of cdk5/p25 (total reaction volume : 100 microliters).

[0076] Inhibitors were solubilised in DMSO (final solvent concentration in the reaction medium, 1%).

[0077] The reaction was stopped with 100 microliters of a solution of 25 g polyphosphoric acid (85% P_2O_5), 126 ml 85% H_3PO_4 , H_2O to 500 ml (diluted to 1:100 before use). An aliquot of the reaction mixture was then transferred to Whatman P81 cation exchange filters and rinsed with the solution described above. Incorporated ^{33}P radioactivity was determined by liquid scintillation spectrometry.

[0078] The cdk5/p25 inhibitory activity of the compounds of the present invention are expressed as IC_{50} values. Typically, 3-fold serial dilutions of the inhibitor over at least a 1000-fold concentration range are used.

[0079] As an illustration the range of IC_{50} 's of the compounds in table 1 is between 200 nanomolar to 5 micromolar concentrations.

Formulation Example

(1) Tablets

[0080] The ingredients below were mixed by an ordinary method and compressed by using a conventional apparatus.

Compound of Example 1	30 mg
Crystalline cellulose	60 mg
Corn starch	100 mg
Lactose	200 mg
Magnesium stearate	4 mg

(2) Soft capsules

[0081] The ingredients below were mixed by an ordinary method and filled in soft capsules.

Compound of Example 1	30 mg
Olive oil	300 mg
Lecithin	20 mg

(1) Parenteral preparations

[0082] The ingredients below were mixed by an ordinary method to prepare injections contained in a 1 ml ampoule.

Compound of Example 1	3 mg
Sodium chloride	4 mg
Distilled water for injection	1 ml

Industrial Applicability

[0083] The compounds of the present invention have GSK3 β or GSK3 α and cdk5/p25 inhibitory activity and are useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of diseases caused by abnormal activity of GSK3 β or GSK3 α and cdk5/p25 and more particularly of neurodegenerative diseases.

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R5 represents a hydrogen atom, a C₁₋₆ alkyl group or a halogen atom; with the proviso that when R3 and R4 represent each a hydrogen atom then R5 is not a hydrogen atom;

When m equals 0, p equals 1 or 2,
When m equals 1, p equals 0, 1 or 2,
When m equals 2, p equals 0 or 1;
and
n represents 0 to 3.

2. A pyrimidone derivative or a salt thereof, or a solvate thereof or a hydrate thereof according to claim 1, wherein R1 represents an unsubstituted pyridinyl group.

3. A pyrimidone derivative which is selected from the group consisting of:

- 9-[3-(2-fluorophenyl)-propyl]-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one
- 9-(2-Oxo-2-phenyl-ethyl)-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one
- 9-(2-Hydroxy-2-phenyl-ethyl)-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one
- 9-(2-Oxo-2-phenyl-ethyl)-7,7-difluoro-2-pyridin-4-yl-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one
- (-)-(S)-9-(2-Hydroxy-2-phenyl-ethyl)-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one
- 9-(2-Oxo-2-phenyl-ethyl)-3-fluoro-7,7-difluoro-2-pyridin-4-yl-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one
- 9-[2-Oxo-2-(3-chlorophenyl)-ethyl]-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one
- (-)-(S)-9-(2-Hydroxy-2-phenyl-ethyl)-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one
- 9-[2-Oxo-2-(3-fluorophenyl)-ethyl]-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one
- 9-[2-Hydroxy-2-(3-chlorophenyl)-ethyl]-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one
- 9-[2-Hydroxy-2-(3-fluorophenyl)-ethyl]-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one
- (-)-(S)-9-(2-Hydroxy-2-phenyl-ethyl)-3-fluoro-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one
- 9-[2-Oxo-2-(4-fluorophenyl)-ethyl]-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one
- 9-[2-Oxo-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl)-ethyl]-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one
- 9-[2-Oxo-2-(3-methoxyphenyl)-ethyl]-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one
- 9-[2-Oxo-2-(4-phenylphenyl)-ethyl]-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one

din-4-one

- 9-[2-(1-Methyl-2-oxo-2-(3,4-methylenedioxy-5-methoxyphenyl)-ethyl)]-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
- 9-[2-Oxo-2-(4-chlorophenyl)ethyl]-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
- 9-[2-Oxo-2-(naphth-2-yl)-ethyl]-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
- 9-[2-Oxo-2-(4-methylphenyl)-ethyl]-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
- 9-(2-Oxo-2-phenyl-ethyl)-7,7-dimethyl-3-bromo-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
- (-)-(S)-9-(2-Methoxy-2-phenyl-ethyl)-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
- 9-(3-Phenyl-propanoyl)-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
- 9-(2-Hydroxy-2-methyl-2-phenyl-ethyl)-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
- 9-(2-methoxy-2-phenyl-2-trifluoromethyl-ethanoyl)-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
- 9-(2-hydroxy-2,2-diphenylethyl)-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
- 9-(2-Hydroxyimino-2-phenyl-ethyl)-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
- 9-(2-Hydroxy-2-methyl-2-phenyl-ethyl)-7,7-dimethyl-3-fluoro-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
- 7,7-dimethyl-9-(2-phenyl-[1,3]dioxolan-2-ylmethyl)-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
- 9-(2,3-dihydroxypropyl)-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
- (-)-(R)-9-(2-methoxy-2-phenyl-ethyl)-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
- 9-(2-hydroxy-3-phenylaminopropyl)-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
- 9-(2-acetylamino-2-phenyl-ethyl)-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
- 9-(2-Amino-2-phenyl-ethyl)-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
- 9-(2-hydroxy-3-phenoxypropyl)-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
- 9-(2-Oxo-2-phenyl-ethyl)-3-fluoro-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one

- 9-[2-Oxo-2-(3-fluorophenyl)-ethyl]-3-fluoro-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
 - 9-(2-Oxo-2-phenyl-ethyl)-3-methyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
 - 9-(2-Oxo-2-phenyl-ethyl)-3-chloro-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
 - 9-(2-Oxo-2-phenyl-ethyl)-3-bromo-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
 - 2-(7-Methyl-6-oxo-8-pyridinyl-3,4-dihydro-2*H*,6*H* pyrimido[1,2-*a*]pyrimidin-1-yl)-*N*-phenyl-acetamide
 - (-)-(S)-9-(2-Hydroxy-2-phenyl-ethyl)-3-chloro-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
 - (-)-(S)-9-(2-Hydroxy-2-phenyl-ethyl)-3-methyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
 - (-)-(S)-9-(2-hydroxy-ethyl)-3-fluoro-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
 - (+)-(S)-9-(2-methoxy-2-phenyl-ethyl)-3-fluoro-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
 - (-)-(R)-9-(2-methoxy-2-phenyl-ethyl)-3-fluoro-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
 - 9-[3-(2-Fluorophenyl)propyl]-7-hydroxy-2-pyridin-4-yl-6,7,8,9-tetrahydro 4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
 - 9-[3-(2-Fluorophenyl)propyl]-7-methoxy-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
 - 9-(2-Oxo-2-phenyl-ethyl)-7-methyl-2-pyridin-4-yl-6,7,8,9-tetrahydro 4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
 - 9-(2-Hydroxy-2-phenyl-ethyl)-7-methyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
 - 9-(2-Hydroxy-2-methyl-phenyl-ethyl)-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
 - 9-(2-Hydroxy-2-methyl-2-phenyl-ethyl)-7,7-dimethyl-2-pyridin-4-yl-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one
- or a salt thereof, or a solvate thereof or a hydrate thereof.

4. A pyrimidone derivative which is selected from the group consisting of:

- [3-(2-Fluoro-phenyl)-propyl]-2,2-dimethyl-7-pyridin-4-yl-2,3-dihydro-1*H*-imidazo[1,2-*a*]pyrimidin-5-one
- [2-Oxo-2-phenylethyl]-2,2-dimethyl-7-pyridin-4-yl-2,3-dihydro-1*H*-imidazo[1,2-*a*]pyrimidin-5-one
- [2-Hydroxy-2-phenylethyl]-2,2-dimethyl-7-pyridin-4-yl-2,3-dihydro-1*H*-imidazo[1,2-*a*]pyrimidin-5-one
- [2-Oxo-2-(4-chlorophenyl)ethyl]-2,2-dimethyl-7-pyridin-4-yl-2,3-dihydro-1*H*-imidazo[1,2-*a*]pyrimidin-5-one
- [2-Oxo-2-(4-methylphenyl)ethyl]-2,2-dimethyl-7-pyridin-4-yl-2,3-dihydro-1*H*-imidazo[1,2-*a*]pyrimidin-5-one
- [2-Oxo-4-phenylphenyl]-2,2-dimethyl-7-pyridin-4-yl-2,3-dihydro-1*H*-imidazo[1,2-*a*]pyrimidin-5-one
- [1-Methyl-3-methoxy-2-(3,4-methylenedioxy-5-methoxyphenyl)-ethyl]-2,2-dimethyl-7-pyridin-4-yl-2,3-dihydro-1*H*-imidazo[1,2-*a*]pyrimidin-5-one

- [2-Oxo-2-(naphth-2-yl)-ethyl]-2,2-dimethyl-7-pyridin-4-yl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one
- [2-Oxo-2-(4-fluorophenyl)-ethyl]-2,2-dimethyl-7-pyridin-4-yl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one
- [2-Oxo-2-(3-methoxyphenyl)-ethyl]-2,2-dimethyl-7-pyridin-4-yl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one
- [2-Oxo-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl)-ethyl]-2,2-dimethyl-7-pyridin-4-yl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one

or a salt thereof, or a solvate thereof or a hydrate thereof.

5. A medicament comprising as an active ingredient a substance selected from the group consisting of a pyrimidone derivative represented by formula (I) or salts thereof, or a solvate thereof or a hydrate thereof according to claim 1.
6. A GSK3 β or GSK3 β and cdk5/p25 inhibitor selected from the group of a pyrimidone derivative represented by formula (I) or salts thereof, or a solvate thereof or a hydrate thereof according to claim 1.
7. Use of a compound according to claims 1 to 4 for the preparation of a medicament for preventive and/or therapeutic treatment of a disease caused by abnormal GSK3 β or GSK3 β and cdk5/p25 activity.
8. Use of a compound according to claims 1 to 4 for the preparation of a medicament for preventive and/or therapeutic treatment of a neurodegenerative disease.
9. Use of a compound according to claim 8, wherein the neurodegenerative disease is selected from the group consisting of Alzheimer's disease, Parkinson's disease, tauopathies, vascular dementia; acute stroke, traumatic injuries; cerebrovascular accidents, brain cord trauma, spinal cord trauma; peripheral neuropathies; amyotrophic lateral sclerosis; retinopathies or glaucoma.
10. Use of a compound according to claims 1 to 4 for the preparation of a medicament for preventive and/or therapeutic treatment of non-insulin dependent diabetes; obesity; manic depressive illness; schizophrenia; alopecia; smoking cessation; epilepsy; or cancers.
11. Use according to claim 10 wherein cancer is breast cancer, non-small cell lung carcinoma, thyroid cancer, T or B-cell leukemia or virus-induced tumor.



European Patent
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EUROPEAN SEARCH REPORT

Application Number
EP 01 40 2432

DOCUMENTS CONSIDERED TO BE RELEVANT			
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Place of search MUNICH		Date of completion of the search 8 November 2001	Examiner Kyriakakou, G
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**ANNEX TO THE EUROPEAN SEARCH REPORT
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